Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

July 8, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0133; Electronic Record; Electronic Signatures; Public Meeting; 69 Federal Register 18591; April 8, 2004

Dear Sir/Madam:

The following comments on the above noted docket are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2003, our members invested over $34 billion in the discovery and development of new medicines.

PhRMA strongly supports this risk-based approach as realistic and a more effective way to protect public health, but because Part 11 applies to all the Food and Drug Administration (FDA) centers and the Office of Regulatory Affairs there remains much to be done. Integrating risk based processes into Part 11 computer system validation, audit trails, and electronic data retention will take time and this reality should be clearly recognized in FDA's plans for future guidance, enforcement and internal training.

PhRMA is a founding member of the Industry Coalition on 21 CFR Part 11, a group of 14 trade associations that have engaged FDA in a dialogue on regulatory and compliance issues associated with this regulation over the past three years. Although the public meeting did not take place because of unforeseen circumstances, PhRMA supports the Coalition's presentation that was forwarded to the FDA prior to the meeting.

As PhRMA has commented to FDA on a number of occasions, the current Part 11 regulation is problematic. It is too prescriptive in terms of technology that should be used. The interpretation of specific portions of the regulation is problematic. Finally, the estimated cost of compliance, including full remediation of non-compliant computer systems, is extraordinarily high. A survey of PhRMA member companies in 2002 indicated that for the pharmaceutical industry alone, compliance costs were likely to be greater than $2 billion. PhRMA believes that this investment would have little impact on product quality.

While the FDA Part 11 regulation was one of the first federal attempts to regulate the new electronic workplace environment, subsequent Federal law and interpretation provides important direction as to how Part 11 can be re-framed.

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Pharmaceutical Research and Manufacturers of America

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3533• FAX: 202-835-3597 • E-Mail: agoldham@phrma.org

- Government Paperwork Elimination Act (GPEA), Pub. L. No. 105-277, §§1701-1710 (1998)
- "Electronic Records and Signatures in Global and National Commerce Act" (E-SIGN) (Pub.L. 106-229, § 1 (2000)

In accordance with the Office of Management and Budget Guidance on GPEA, agency considerations of cost, risk, and benefit, as well as any measures taken to minimize risks, should be commensurate with the level of sensitivity of the transaction. Low-risk information processes may need only minimal safeguards, while high-risk processes may need more. In the context of legal and litigation risks, "low-risk information processes" are those that have a small chance of generating significant liability, financial impact, or litigation that would have a significant effect on the agency.

FDA is already moving towards a risk-based approach to compliance with the evolution of Process Analytical Technology (PAT) that is part of the GMP for the 21st Century initiative. This same paradigm should be followed for Part 11. Thus, there are three important concepts that must be followed:

1. Control mechanisms for e-records should be applied proportional to the impact of the record on the public health.
2. A hierarchical approach to implementation for applications, data and reports should be used similar to the Scale Up and Post-Approval Changes guidances (SUPAC).
3. A benefit-driven approach acceptable to FDA and the regulated industries must be developed.

PhRMA supported the new scope and application of Part 11 Guidance that FDA published last summer. However, the Agency must now take the next step and revise the underlying regulation so that the precepts set forth in the Guidance are reflected in the rule itself. The following issues should be addressed as this process moves forward:

- Don't limit use of risk based approach.
- Organizations should be allowed to apply their risk based approach to any area of electronic records.
- There are a multitude of risk-based approaches and tools.
- FDA should not specify any particular approach or tools to be used.
- If a risk based approach is used then it should be defined and documented.

These meet the FDA criterion as set forth in the Scope Guidance:

> "We (FDA) recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity " [Lines 207-209]

Thus, PhRMA recommends that the rule either be rescinded and that FDA rely on recently passed Federal legislation that enables companies to utilize electronic records and signatures as part of the "business" they do with FDA or that it be dramatically abbreviated to achieve the same goal. Specific regulatory aspects of electronic records and signatures can be adequately dealt with through guidance documents such as the above-mentioned Scope Guidance.

The remainder of this letter details PhRMA's specific points with respect to the questions FDA has posed.

Part 11, Subpart A – General Provisions

1. We are interested in comments on FDA's interpretation of the narrow scope of Part 11 as discussed in the Part 11 guidance and whether Part 11 should be revised to implement the narrow interpretation described in the guidance.

Yes, the regulation should be modified to conform to the principles outlined in the guidance. As FDA is aware, guidance documents reflect the Agency's best thinking on a regulatory matter but do not have the same legal underpinning as a regulation. As PhRMA has commented to FDA in the past, Part 11 needs to be re-written so that it is risk-based and allows the regulated industry the ability to implement practices that address record authenticity and security as appropriate. In addition, the regulation needs to be clear that compliance issues can be addressed by a combination of hardware, software, and procedural controls.

2. We are interested in comments on whether revisions to definitions in Part 11 would help clarify a narrow approach and suggestions for any such revisions.

As noted above, the critical issue is what regulatory requirements are being addressed. Over the years, the evolution of many of the GxP regulations has specified the needs for a signature, audit trail, and/or retention time period. Compliance with these predicate rules should be technology neutral. Thus, the underlying Part 11 regulation can be markedly revised to reflect that FDA will accept electronic records in lieu of paper records. However, the regulation needs to identify what constitutes a record subject to the regulation. The current definition in 21 C.F.R. §11.3(b)(6) is so broad that much of the preamble is spent trying to explain exceptions that were not intended to be included. A new term such as "FDA record," "Part 11 record," "regulated record" or some similar term needs to be defined and then used within the body of the regulation. The new definition needs to encompass the intended aspects of narrow scope as well as defining when the regulated record begins (i.e., when does a document or data become a record). The regulation should draw a distinction between data versus documents. It is important to distinguish those few cases where first recording of raw data must be maintained, versus the vast majority of cases where there is no such expectation. The definition should make it clear that draft documents are not regulated records, and that documents do not become regulated records until the first signature is applied or until they are released for their intended use (if not signed).

3. We are interested in comments on the need for clarification in Part 11 regarding which records are required by predicate rules and are therefore required to be Part 11 compliant.

Revising Part 11 should be taken on with the goal of simplifying the regulation. The phrase "required by predicate rule" needs to be clarified. Does it mean "explicitly required," or does it include "implicitly required records that are used to demonstrate compliance" to the Agency. In the past there have been multiple conflicting interpretations from different Agency representatives. If Part 11 is only intended to apply to explicit predicate rule record keeping requirements, that should be very clearly stated.

Part 11, Subpart B – Electronic Records

1. We are interested in comments on whether there are other areas of Part 11 that should incorporate the concept of a risk-based approach, detailed in the Part 11 Guidance (e.g., those that require operational system and device checks).

The regulation should be kept simple and not prescriptive. All areas of Part 11 should be subject to a risk-based approach. It is more appropriate to address these issues in guidance as opposed to regulation as technology is constantly evolving. As has been seen in the GMP area, attempts at being too prescriptive in regulation act as a disincentive to adopt new technologies.

2. Is additional clarity needed regarding how predicate rule requirements related to subpart B can be fulfilled?

No, the regulation should not be prescriptive.

3. Should the requirements for electronic records submitted to FDA be separate from electronic records maintained to satisfy predicate rule requirements?

No, there should be one uniform and consistent approach to electronic records.

4. Should Part 11 continue to differentiate between open systems and closed systems?

Yes, each of these systems is different, but it is important to note that a risk assessment approach to compliance will address the relevant issues.

Individual Controls in Subpart B

1. Should we retain the validation provision under § 11.10(b) required to ensure that a system meets predicate rule requirements for validation?

The question is not "predicate rule requirements for validation," but rather validating to continue to meet general predicate rule expectations. Most of the predicate rules do not have an explicit computer validation requirement. Therefore, absent the validation required by Part 11, many regulated computer systems would not be validated at all except for business reasons.

If retained, any computer validation requirement should be risk-based. Computer validation is expensive and can be overly complex. A variable approach based on patient risk posed by the system is preferred.

2. Are there any related predicate rule requirements that you believe are necessary to preserve the content and meaning of records with respect to record copying and record retention? What requirements would preserve record security and integrity and ensure that records are suitable for inspection, review, and copying by the agency?

Long term record retention and record copying are two of the most contentious and technically difficult provisions of current Part 11. The industry should not be put in the position of having to retain outdated technology for the sole purpose of providing an electronic copy to the FDA. If such retention is required, the timeframe should be very limited. As allowed by the FDA guidance on Scope and Application, archiving to paper should be retained as a viable alternative, with appropriate procedural controls to reasonably assure authenticity and accuracy.

3. Should audit trail requirements include safeguards designed and implemented to deter, prevent, and document unauthorized record creation, modification, and deletion?

Such requirements need to be based on the predicate rules and a risk assessment of the trustworthiness of the record.

4. Should Part 11 be modified to incorporate concepts, such as configuration and document management, for all of a systems software and hardware?

No, this is already a part of software validation.

Part 11 Subpart C – Electronic Signatures

1. Should Part 11 address investigations and follow up when these security breaches occur?

No this is an issue related to any type of breach of Standard Operating Procedures (SOP) and is not restricted to electronic signatures.

Additional Questions for Comment

1. What are the economic ramifications of modifying Part 11 based on the issues raised in this document?

It is premature to conjecture the full impact of a change in the Part 11 regulation. PhRMA believes that a significant amount of the cost estimates from our earlier survey will not need to be committed if the Agency moves to a risk-based implementation.

2. Is there a need to clarify in Part 11 which records are required by predicate rules where those records are not specifically identified in predicate rules? If so, how could this distinction be made?

Yes, the key is for the Agency to define what they mean by "required by predicate rule." How can something be "required by" when it is not "written in" the predicate rule? The issue of explicit versus implicit requirement needs to be clarified.

3. In what ways can Part 11 discourage innovation?

The regulation should not prescribe what approaches companies should take. Issues related to record authenticity and security can be addressed by a combination of hardware, software, and procedural controls. Regulations should not dictate how a company meets their obligations in this regard.

4. What potential changes to Part 11 would encourage innovation and technical advances consistent with the agency's need to safeguard public health?

FDA should move towards a risk-based approach for regulation in this area.

5. What risk-based approaches would help to ensure that electronic records have the appropriate levels of integrity and authentic elements and that electronic signatures are legally binding and authentic?

Implementation should be left up to the companies. PhRMA is already working on a standard for secure electronic signatures. Our Secure Access for Everyone (SAFE) initiative uses a combination of hardware, software, and procedural controls to embed a secure electronic signature in an electronic record. This project is currently in the proof of concept stage that will be completed before the end of the year.

6. What are stakeholder concerns in regards to modifications made to legacy systems in use as of August 1997?

PhRMA has commented on this issue to FDA in the past. Some of these systems are extremely old and cannot be easily updated; in fact, some systems may not be able to be modified at all. There may not be a sound business case to update the system. A proper risk assessment of the legacy system as it fits into the overall process that is being looked at will suggest how this issue should be managed.

7. Should Part 11 address record conversion?

PhRMA is unsure about the nature of this question. Does FDA refer to the conversion of paper records to electronic format (such as scanning an image to a PDF file) or the long term maintenance of electronic records and the possible need to convert the record to take into account software updates?

8. Are there provisions of Part 11 that should be augmented, modified, or deleted as a result of new technologies that have become available since Part 11 was issued?

Yes, the regulation should be markedly modified so that the principal focus is on the general acceptability of electronic records. The Agency can communicate its expectations through the issuance of appropriate guidance documents. If there are specific needs for a given regulation these should be dealt with in the predicate rule rather than in one overarching regulation that covers all electronic records.

PhRMA hopes these comments are useful to FDA as the Agency moves forward on this critical issue.

Sincerely,